Co-infection with Group A *Streptococci* and *Epstein-Barr* Virus Presenting with Acute Glomerulonephritis and Acute Left Ventricular Dysfunction

Tamami Watanabe, Hitoshi Sugawara, Hiroyuki Tamura, Akira Ishii, Hiroshi Matsubayashi, Masafumi Kakei and Shin-ichi Momomura

**Abstract**

Acute pharyngitis is commonly encountered, but a definite etiological diagnosis is difficult. Although co-infection with Group A *Streptococci* (GAS) and *Epstein-Barr* virus (EBV) is uncommon, general physicians should consider the possibility of EBV co-infection in patients with GAS pharyngitis who fail to show prompt remission of symptoms following appropriate antibiotic treatment. In this article, we present a rare case of a 16-year-old girl who had co-infection with GAS and EBV. She developed acute glomerulonephritis and left ventricular dysfunction in an overlapping manner. We were able to follow her until she healed, and herein describe the pathogenesis of her systemic and pulmonary edema.

**Key words:** group A streptococci, *Epstein-Barr* virus (EBV), infectious mononucleosis, acute glomerulonephritis, acute left ventricular dysfunction


**Introduction**

A sore throat with a fever is among the most common of symptoms that prompt a visit to the physician. However, a definite etiological diagnosis is often difficult. Group A *streptococci* (GAS) and *Epstein-Barr* virus (EBV) are two pathogens that are well-known to cause acute pharyngitis. Both can be complicated by glomerulonephritis and myocarditis (1, 2). Co-infection with GAS and EBV has rarely been reported in immunocompetent adolescents.

We herein report the case of a patient who was diagnosed to have co-infection with GAS and EBV; she presented with systemic edema, orthopnea, and acute pulmonary edema, which worsened after admission. We were able to treat her successfully and follow her until confirmation of the absence of proteinuria, a return to normal of the serum brain natriuretic peptide (BNP) level and echocardiographic findings, and positive conversion of anti-EBV-associated nuclear antigen antibodies.

We herein report the pathogenesis of co-infection with GAS and EBV and the mechanism underlying the development of systemic symptoms and pulmonary edema in association with left ventricular dysfunction.

**Case Report**

A 16-year-old Japanese high school student presented with a 38°C fever and generalized fatigue 26 days before the admission. The symptoms subsided within a week with treatment for a common cold prescribed by a local physician. She again presented with fever (of 37°C) and cough 16 days before the admission, and five days later, developed enlarged tonsils, rhinorrhea, and bilateral leg edema. Seven days before the admission (four days after the above symptoms developed), she had tried an anti-allergic drug to treat the nasal symptoms, but the drug was not effective. She subsequently started taking clarithromycin (200 mg, twice a day), dimemorfan (10 mg, three times a day), d-chlorpheniramine (2 mg, three times a day), and ibuprofen (100 mg, three times a day) at another hospital four days before she was admitted to our institution; however, the
When she was admitted to our medical center for further examinations, she reported a body weight gain of 7.4 kg during the previous 2 weeks. Her body temperature was 37.9°C, blood pressure was 145/103 mmHg, pulse rate was 103/min and regular, respiratory rate was 20 times per minute, and the percutaneous oxygen saturation under room air was 92%.

A physical examination revealed throat congestion, bilateral enlarged tonsils without white moss, small multiple tender cervical lymphadenopathies in both the anterior and posterior triangles, and peripheral pitting edema. We could not detect any pulmonary rales, heart murmur, splenomegaly, axillary lymphadenopathy, or inguinal lymphadenopathy.

The laboratory findings (Table 1) were as follows: peripheral blood leukocytosis was present, with many atypical lymphocytes, hypoalbuminemia, elevated liver enzyme levels, a normal creatine kinase (CK) level, elevated serum C-reactive protein, low C3, a positive test for anti-streptolysin O (ASO) antibodies, negative serum test for anti-nuclear antibodies, and an elevated BNP level. The serum creatinine level was normal. A urinalysis showed 3+ proteinuria and microscopic hematuria. Both the rapid diagnostic test and culture of the throat swab were positive for GAS, which was found to show sensitivity to penicillin and cephalosporin antibiotics. The results of the serological tests were positive for acute EBV infection. The serum test for anti-EBV-associated nuclear antigen (EBNA) antibody was negative, while that for the anti-EBV capsid antigen (VCA) Immunoglobulin G (IgG) was positive, and the peripheral blood EBV-DNA titer was $1.8 \times 10^4$ copies/10^6 cells. Based on these findings, the patient was diagnosed to have a concomitant streptococcal infection and infectious mononucleosis.

A plain chest X-ray revealed evidence of cardiomegaly and pulmonary edema (Fig. 1A). An electrocardiogram showed low-voltage QRS complexes in the limb leads. Echocardiography revealed evidence of left ventricular dysfunction, characterized by a low ejection fraction (EF), short deceleration time, small pericardial effusion, and hypokinesis of a part of the left ventricular posterior wall.

Her clinical diagnosis was acute glomerulonephritis and congestive heart failure due to acute left ventricular dysfunction. She was started on treatment with ceftriaxone sodium (CTRX, 2 g every 24 hours) based on its bactericidal effect against Streptococci, and clindamycin (CLDM, 450 mg every 8 hours) to inhibit the production of toxin. The response to furosemide was poor, and the pulmonary edema worsened (Fig. 1B), and the orthopnea persisted. Therefore, extracorporeal ultrafiltration was carried out on hospital day (HD) 4 to improve the water balance.

Based on the results of the microbial sensitivity tests, the antibiotics were switched to cefotiam hexetil hydrochloride (CTM-HE, 400 mg every 12 hours) on HD 5, which was continued for 14 days. The count of atypical lymphocytes on the peripheral blood smear peaked on HD 5. With a reduction of the proteinuria, the body weight of the patient re-
turned to the baseline value. Her orthopnea resolved on HD 10. The patient was then started on furosemide (20 mg/day), perindopril (1 mg/day), and carvedilol (1.25 mg/day) on HD 21; she was discharged on HD 22 (Fig. 2).

The patient visited us regularly for follow-up examinations. The serum BNP returned to normal, and evidence of cardiomegaly on the plain chest X-ray (Fig. 1C) was no longer present by day 53 after discharge (AD), and the urinary protein level also became undetectable by day 98 AD. Positive conversion of anti-EBNA antibodies was confirmed on day 161 AD. The echocardiographic findings normalized by day 224 AD, and the microscopic hematuria resolved by day 291 AD (Table 2). Furosemide, perindopril, and carvedilol were tapered, and could be discontinued by one year AD. The patient eventually showed a complete recovery from the illness.

Discussion

The present case underscores three important clinical issues. First, such co-infection with EBV and GAS is very rare in immunocompetent adolescents. Rush et al. reported that 18% of 222 patients (age, 1-20 years) diagnosed as having EBV were previously confirmed to be positive for GAS (3). Henke et al. similarly commented that 29% of more than 700 patients up to 25 years old with EBV illness had co-infection with GAS pharyngitis (4). In contrast, Chretien et al. reported, from a prospective study of 150 college students with infectious mononucleosis, that only 2.4% showed positive throat cultures for GAS (5). To the best of our knowledge, the rate of co-infection in adolescents remains unclear. In patients diagnosed to have GAS pharyngitis who do not show prompt remission with appro-
Acute left ventricular dysfunction. To determine the etiology of these disorders, a pathological diagnosis of both the kidneys and myocardium may be necessary. We assigned a higher priority to obtaining improvement of the patient's clinical condition than for obtaining materials for pathological examination. However, based on the clinical presentation, we presume that the acute glomerulonephritis occurred first, and the acute left ventricular dysfunction developed in an overlapping manner (Fig. 3), because the urinary protein excretion level promptly decreased after admission, and the peak count of atypical lymphocytes and exacerbation of heart failure occurred virtually simultaneously several days after admission.

Acute glomerulonephritis is characterized by hematuria, edema and hypertension, frequently accompanied by oliguria and decreased glomerular filtration. We considered that the acute left ventricular dysfunction in our patient may have been caused by both transient hypertensive heart disease and volume overload resulting from the decreased glomerular filtration due to the acute glomerulonephritis. We also speculated that the decreased glomerular filtration and left ventricular dysfunction exacerbated the systemic and pulmonary edema synergistically (Fig. 3).

GAS and EBV have been reported to have the ability to induce the development of both glomerulonephritis and myocarditis. Most systems and organs, especially the heart muscle, are affected in patients with EBV infection. According to one study of 190 children with EBV infection, the frequency of myocarditis was 2.6% (1). EBV has also been implicated as a rare cause of glomerulonephritis (6, 7). To the best of our knowledge, there is no case report in the literature of a patient similar to ours, who developed critical complications in both the kidneys and heart caused by co-infection with GAS and EBV.

The third important clinical implication of the present study was that we were able to follow the patient for a long period after discharge, until she had completely recovered. It became obvious that the abnormalities resolved in the following sequence: normalization of BNP, resolution of proteinuria, positive conversion of anti-EBNA antibodies, normalization of the echocardiographic findings, and resolution of the microscopic hematuria.

In conclusion, our patient had a co-infection with GAS and EBV, and presented with disorders of two major systems: namely, acute glomerulonephritis and acute left ventricular dysfunction. Although acute pharyngitis with a high fever is a commonly encountered condition in clinical practice, it may be necessary to conduct an evaluation for possible EBV co-infection; the converse would also be valid.

Second, co-infection with EBV and GAS may cause multisystem disorders, such as acute glomerulonephritis and acute left ventricular dysfunction. To determine the etiology of these disorders, a pathological diagnosis of both the kidneys and myocardium may be necessary. We assigned a higher priority to obtaining improvement of the patient’s clinical condition than for obtaining materials for pathological examination. However, based on the clinical presentation, we presume that the acute glomerulonephritis occurred first, and the acute left ventricular dysfunction developed in an overlapping manner (Fig. 3), because the urinary protein excretion level promptly decreased after admission, and the peak count of atypical lymphocytes and exacerbation of heart failure occurred virtually simultaneously several days after admission.

Table 2. The Time Course of the Improvement of Clinical Indicators

<table>
<thead>
<tr>
<th>Days after discharge (days)</th>
<th>-22</th>
<th>-8</th>
<th>-2</th>
<th>7</th>
<th>28</th>
<th>53</th>
<th>98</th>
<th>161</th>
<th>224</th>
<th>291</th>
<th>701</th>
<th>777</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>0.88</td>
<td>0.67</td>
<td>0.58</td>
<td>0.74</td>
<td>0.64</td>
<td>0.56</td>
<td>0.57</td>
<td>0.58</td>
<td>0.63</td>
<td>0.58</td>
<td>0.58</td>
<td>0.58</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>956</td>
<td>782</td>
<td>279</td>
<td>36</td>
<td>11</td>
<td>6</td>
<td>8</td>
<td>5.7</td>
<td>&lt;4.0</td>
<td>&lt;4.0</td>
<td>&lt;4.0</td>
<td>&lt;4.0</td>
</tr>
<tr>
<td>EBV-DNA (copies/10⁶ cells)</td>
<td>1.8×10⁴</td>
<td>3.6×10³</td>
<td>1.8×10³</td>
<td>5.1×10²</td>
<td>6.2×10²</td>
<td>&lt;2.0×10²</td>
<td>&lt;2.0×10²</td>
<td>&lt;2.0×10²</td>
<td>&lt;2.0×10²</td>
<td>&lt;2.0×10²</td>
<td>&lt;2.0×10²</td>
<td>&lt;2.0×10²</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>3+</td>
<td>1+</td>
<td>1+</td>
<td>2+</td>
<td>1+</td>
<td>1+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>0.88</td>
<td>0.67</td>
<td>0.58</td>
<td>0.74</td>
<td>0.64</td>
<td>0.56</td>
<td>0.57</td>
<td>0.58</td>
<td>0.63</td>
<td>0.58</td>
<td>0.58</td>
<td>0.58</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>956</td>
<td>782</td>
<td>279</td>
<td>36</td>
<td>11</td>
<td>6</td>
<td>8</td>
<td>5.7</td>
<td>&lt;4.0</td>
<td>&lt;4.0</td>
<td>&lt;4.0</td>
<td>&lt;4.0</td>
</tr>
<tr>
<td>EBV-DNA (copies/10⁶ cells)</td>
<td>1.8×10⁴</td>
<td>3.6×10³</td>
<td>1.8×10³</td>
<td>5.1×10²</td>
<td>6.2×10²</td>
<td>&lt;2.0×10²</td>
<td>&lt;2.0×10²</td>
<td>&lt;2.0×10²</td>
<td>&lt;2.0×10²</td>
<td>&lt;2.0×10²</td>
<td>&lt;2.0×10²</td>
<td>&lt;2.0×10²</td>
</tr>
</tbody>
</table>


Figure 3. The pathogenesis of the co-infection with GAS and EBV, and the mechanism underlying the development of systemic and pulmonary edema with left ventricular dysfunction. Both Group A Streptococcus and Epstein-Barr virus can cause acute glomerulonephritis and acute left ventricular dysfunction. Based on the clinical presentation of our patient, the acute glomerulonephritis occurred first, and acute left ventricular dysfunction developed in an overlapping manner. The decreased glomerular filtration likely exacerbated the systemic and pulmonary edema synergistically with the left ventricular dysfunction. EBV: Epstein-Barr virus, GAS: Group A Streptococci, AGN: acute glomerulonephritis
The authors state that they have no Conflict of Interest (COI).

References


© 2012 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html